

Potential Risk Factors for Nivolumab-induced Thyroid Dysfunction

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Abstract. *Background:* Thyroid dysfunction is occasionally reported after the administration of nivolumab. We report on the incidence of and risk factors for nivolumab-induced thyroid dysfunction in patients with non-small lung cancer. *Patients and Methods:* A total of 82 patients who received nivolumab between January 2016 and December 2016 at the Kanagawa Cancer Center were included. Prior to nivolumab treatment, 72 patients had normal thyroid function. *Results:* Among the 72 patients with normal thyroid function prior to nivolumab treatment, the incidence of thyroid dysfunction was 19.5%. There were no significant differences between patients in whom thyroid dysfunction had occurred regarding sex, age, nivolumab dose, or thyroid function prior to nivolumab administration. However, the total number of doses of nivolumab was significantly greater in patients who developed thyroid dysfunction after nivolumab treatment ($p=0.03$). *Conclusion:* The total number of doses administered may be a risk factor for the development of thyroid dysfunction after nivolumab therapy.

Nivolumab is an monoclonal antibody specific for programmed cell death-1 (PD-1) that is used in the treatment of cancer such as malignant melanoma, non-small cell lung cancer (NSCLC), renal cell cancer, and Hodgkin's lymphoma. Thyroid dysfunction, including hypothyroidism

and hyperthyroidism, is occasionally reported after the administration of nivolumab. However, the association between thyroid dysfunction and nivolumab remains unclear. In this retrospective study, we report on the incidence of and risk factors for thyroid dysfunction following nivolumab treatment.

Materials and Methods

Eighty-two patients who received nivolumab between January 2016 and December 2016 at Kanagawa Cancer Center were included. Baseline patient characteristics are shown in Table I. All patients had a diagnosis of NSCLC. Prior to nivolumab treatment, 72 patients had normal thyroid function, seven had subclinical hypothyroidism, defined as an elevated thyrotropin level with free thyroxine level within the reference range, and three had subclinical hyperthyroidism, defined as an decreased thyrotropin (TSH) level with free thyroxine (F-T4) level within the reference range. In this group, some patients had started treatment with oral levothyroxine prior to the administration of nivolumab. Nivolumab was administered intravenously at 3 mg/kg once every 2 weeks. Statistical analysis was performed using the Chi-square test and Student's *t*-test.

Results

Among the 72 patients with normal thyroid function prior to nivolumab treatment, the incidence rate of nivolumab-induced thyroid dysfunction was 15.3% (11 patients) for hyperthyroidism and subclinical hyperthyroidism, and 4.2% (3 patients) for hypothyroidism and subclinical hypothyroidism. Among the 10 patients with thyroid dysfunction prior to nivolumab treatment, no patient developed overt thyroid dysfunction after nivolumab treatment. Table II shows patient characteristics, grouped according to whether thyroid dysfunction was observed following nivolumab treatment. No significant differences

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were observed regarding sex, age, nivolumab dose, or thyroid function prior to nivolumab administration between the two groups. However, the total number of doses was significantly greater in patients who developed thyroid dysfunction after nivolumab treatment ($p=0.03$). Among the 14 patients who developed thyroid dysfunction, the median number of days until thyroid dysfunction was manifested was 81, with a range of 13 days to approximately 6 months. Three patients required medication for their condition, and all subsequently recovered from their thyroid dysfunction (Table III). Two patients required methimazole treatment for elevated free thyroxine. No patient developed overt hypothyroidism, but one patient required levothyroxine treatment for elevated TSH.

Discussion

In Japan, nivolumab is used for malignant melanoma, which cannot be cured, for non-curable progression or recurrence of NSCLC, unresectable or metastatic renal cell carcinoma, and recurrent or refractory Hodgkin's lymphoma. In this study, all patients had a diagnosis of NSCLC. According to the all examples survey in Japan, nivolumab was administered from the time of approval to 631 patients by March 2015. Thyroid dysfunction was reported in 44 cases. The breakdown was as follows: thyroid dysfunction in 30 cases (4.8%), thyroid disorder in five (0.8%), hyperthyroidism in five (0.8%), goiter in two (0.3%), thyroiditis in one (0.2%), and autoimmune thyroiditis in one case (0.2%) (1).

Although thyroid dysfunction caused by nivolumab has been reported, there are many cases of its use in malignant melanoma. In a phase 2 trial of Japanese patients with advanced malignant melanoma, the most frequently occurring drug-related adverse events were free triiodothyronine (F-T3) decrease, F-T4 decrease, and alkaline phosphatase increase (2). The incidence of nivolumab-induced thyroid dysfunction in malignant melanoma is reported to be in the range of 5.6–39% (3-5). In our study, only patients with NSCLC were included, and the incidence of thyroid dysfunction was approximately 20%. Therefore, this suggests that thyroid dysfunction caused by nivolumab might not depend on the target disease.

Dysfunction of the endocrine system by nivolumab may cause adrenal gland dysfunction or pituitary inflammation. A case of eosinophilia and hyponatremia that developed and was diagnosed as pituitary inflammation using magnetic resonance imaging has been reported (6). Therefore, hypothyroidism associated with decreased pituitary function may also develop. When differentiation is required, adrenocorticotropin and cortisol measurement, pituitary gland imaging, and magnetic resonance imaging are also considered. In this study, hyperthyroidism and subclinical hyperthyroidism (15.3%) were more frequent than

Table I. Baseline patient characteristics.

Characteristic	n=82
Gender	
Male	56 (68%)
Female	26 (32%)
Median age (range)	66.5 (46-84) years
Median single dose (range)	180 (107-240) mg
Median total number of doses (range)	4 (1-22)
Normal thyroid function, n (%)	72 (87.8%)
Subclinical hypothyroidism, n (%)	7 (8.5%)
Subclinical hyperthyroidism, n (%)	3 (3.7%)
Thyroid function	
Median TSH (range)	1.46 (0.04-99.69) mIU/ml
Median F-T3 (range)	2.71 (1.42-3.62) pg/ml
Median F-T4 (range)	1.09 (0.48-1.50) ng/ml

TSH: Thyrotropin, F-T3: free triiodothyronine, F-T4: free thyroxine.

Table II. Characteristics of patients with normal thyroid function prior to nivolumab treatment.

Characteristic	Thyroid dysfunction (n=14)	No thyroid dysfunction (n=58)	p-Value
Gender			
Male	7 (50%)	39 (67.2%)	0.23
Female	7 (50%)	19 (32.8%)	
Median age (range)	64 (46-71)	66 (46-84)	0.29
Median single dose (mg)	183.5	176.5	0.36
Median total number of doses (range)	8 (2-18)	4 (1-22)	0.03
Thyroid function			
Median TSH	1.35 mIU/ml	1.46 mIU/ml	0.47
Median F-T3	2.82 pg/ml	2.71 pg/ml	0.30
Median F-T4	1.08 ng/ml	1.09 ng/ml	0.80

TSH: Thyrotropin, F-T3: free triiodothyronine, F-T4: free thyroxine.

hypothyroidism and subclinical hypothyroidism (5.6%). Since patients who developed hypothyroidism after a transient thyrotoxic phase have been reported (7), such cases may have been included.

In general, major adverse events associated with nivolumab treatment occur during the first 6 months after treatment initiation (4). In this study, thyroid dysfunction occurred within this 6-month period. Given that the treatment period of the group that did not develop thyroid dysfunction was approximately only 2 months, the incidence of thyroid dysfunction appears to increase as the treatment period becomes longer. Two cases of subclinical hypothyroidism were reported to have developed overt hypothyroidism after

Table III. Data of patients who developed overt hyperthyroidism/subclinical hyperthyroidism after nivolumab.

Case	Age, years	Gender	Total number of doses	Number of days to onset	TRAb	TgAb	Treatment
1	64	F	3	13	–	+	None
2	64	F	4	20	–	+	Methimazole
3	64	M	17	111	NE	NE	None
4	58	M	3	12	NE	NE	None
5	69	F	12	182	NE	NE	None
6	49	M	11	57	–	–	None
7	46	M	16	140	–	NE	None
8	68	F	2	19	NE	NE	None
9	54	M	4	29	–	+	Methimazole
10	71	M	17	103	NE	NE	None
11	69	M	4	82	–	–	None
12	56	F	8	80	NE	–	None
13	67	F	18	155	NE	+	Levothyroxine
14	68	F	8	126	NE	+	None

TRAb: Thyrotropin receptor antibody, TgAb: thyroglobulin antibody, NE: not examined, –: negative, +: positive.

the start of nivolumab treatment (8). However, in this study, among seven patients with subclinical hypothyroidism prior to nivolumab treatment, no patient developed overt hypothyroidism after administration of nivolumab.

There are few reports that discuss antibodies such as the TSH receptor antibody, thyroglobulin antibody, and thyroid peroxidase antibody before and after administration of nivolumab. It will be interesting to see whether thyroid dysfunction is likely to occur in antibody-positive patients and whether the antibodies will be detected prior to the occurrence of thyroid dysfunction. In this study, the antibody was measured only after thyroid dysfunction occurred. Measurement of antibodies before and after administration may make it possible to clarify the mechanism of occurrence of thyroid dysfunction and the risk factors for developing overt thyroid dysfunction. Thyroid dysfunction due to PD-1 inhibitor is frequently observed. However, there are few cases that exhibit severe thyroid dysfunction that is clinically problematic, and nivolumab treatment is often continued (9). Even in this study, although three out of 14 patients required medication for their condition, all subsequently recovered from their thyroid dysfunction.

Conclusion

Thyroid dysfunction is frequently associated with nivolumab treatment, and the total number of doses may be a risk factor for the development of thyroid dysfunction. Regular measurement of thyroid function is, therefore, necessary during nivolumab treatment, and appropriate treatment of thyroid dysfunction may be required in some cases.

Conflicts of Interest

None declared.

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